REMARKS

Claims 1-25 are pending. Claim 4 is currently amended.

Claim 4 has been amended for clarity as suggested by the Examiner.

The specification has been amended to reflect the publication of the cited U.S. patent application.

§ 112 Rejections

Claim 4 stands rejected under 35 USC § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

In particular, the Patent Office asserts that claim 4 uses the abbreviation "H-bond", and that it would be more effect if the full unabbreviated term is used. For purposes of current examination, H-bonds signify hydrogen bonds.

Applicants submit that the meaning of the term "H-bond" is clear to one of ordinary skill in the art, but for purposes of advancing prosecution Applicants have amended claim 4 for clarity as suggested by the Examiner. It is submitted that the current amendment to claim 4 overcomes the rejection under 35 USC § 112, second paragraph. Reconsideration and withdrawal of the rejection is requested.

§ 103 Rejections

Claims 1-5, 8, and 10-24 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Katz et al. [Journal of Pharmaceutical Sciences, 1965, volume 54, pages 591-594] in view of Loftsson et al. [Drug Development and Industrial Pharmacy, 1994, volume 20, pages 1699-1708] in view of Tayar et al. [Journal of Pharmaceutical Science, volume 80, 1991, pages 590-598].

The Patent office asserts that Katz et al. teach the first step of the body of claim 1 in Table 1 (page 593). Table 1 is said to list molecular weights and partition coefficients for a plurality of molecules.

The Patent Office asserts that molecular weights are deduced from the columns listing the combination of weight by volume concentrations and the molar concentrations. The Patent Office further asserts that partition coefficients are said to be listed in the fifth column of data in Table 1 of Katz et al., thus describing claim 15.

The Patent Office asserts that instant claims 16 and 17 are also described by Table 1 in that McKenzie parameter (p McK-S_{50}) is calculated in the last column as the negative logarithm of dilution producing vasoconstriction of 50% of subjects (Claim 16) while the partition coefficients are experimentally measured (claim 17).

The Patent Office asserts that claims 20-24 are described on page 592, column 2, lines 7-11, which state, "McKenzie and Stoughton... prepared dilutions of the corticosteroids in tenfold dilutions ranging from 1:100 to 1:10,000,000; 0.02 ml of these dilutions were applied to 1-in. areas of the forearm and covered with Saran wrap." Thus, the requirements of skin of a live mammal (claims 20 and 22) are met. The Saran wrap comprises an adhesive patch (claim 23), and the chemical is in contact with the adhesive patch (the Saran wrap) before it penetrates the skin (Claim 24). This entire system comprises a transdermal delivery system (claim 21).

The Patent Office admits that there are two aspects of this rejection that Katz et al. fail to teach: (1) Katz et al. do not teach the compound-excipient formulation of claim 1, the diffusion method and analysis, saturation of the model compound, impact of rotatable and hydrogen bond donors and acceptors, use of a Franz cell(s), a plurality of excipients, utilization of a chemical reaction, use of a synthetic polymer membrane, calculated and empirical parameters of the pharmaceutical, and a transdermal delivery system; and (2) while Katz et al. teach a partition coefficient between ether and water, they do not teach the required partition between octanol and water (log (P) is based on the partition coefficient between octanol and water).

To address the second concern, the Patent Office asserts that Tayar et al. teach the solvation of 121 solutes in five different solvent systems (octanol-water, heptane-water, chloroform-water, diethyl ether-water, and butyl acetate-water) [abstract, page 590], and argues

that it would be obvious to adjust the partition study of Katz et al. from water-ether to water-octanol according to the procedures of this study of Tayar et al. stating "one would simply need to replace the ether with octanol."

To address the first concern, the Patent Office asserts that Loftsson et al. teach a method of making a pharmaceutical composition between hydrocortisone and different cyclodextrins to enhance transdermal delivery. (One of the model compounds listed in Table 1 of Katz et al. is hydrocortisone). The Patent Office asserts that the preamble, and the second and third steps in the body of the claim are thus described. The Patent Office further asserts that Figure 2 of Loftsson et al. teaches a relationship between diffusion through a membrane and cortisone concentration (the fourth body step) and the fifth body step is taught as the combination of the hydrocortisone and each of the cyclodextrins used in the formulation. The Patent Office further asserts that Figure 2 additionally uses a synthetic polymer membrane (cellophane), which describes claim 12.

The Patent Office asserts that claim 2 is described on page 1705 in Loftsson et al. under "Table 1," which is said to show an excess of cyclodextrin concentration used to saturate the hydrocortisone.

The Patent Office asserts that claims 3 and 4 are described on page 1700 of Loftsson et al., lines 21-24, which state, "The molar substitution (MS) i.e. the average number of propylene oxide molecules that have reacted with one glucopyranose unit, was 0.6 or 0.9. HPβCD has a very good aqueous solubility (over 60% w/v) and forms stable complexes with many drugs." Thus, the type of molar substitution chosen for the cyclodextrin affects its size, number of rotatable bonds, and hydrogen bonding characteristics.

The Patent Office asserts that claims 5, 8, 13, and 14 are described in Loftsson et al. on page 1702, the sixth and seventh lines from the bottom of the page which state, "Female hairless mice were killed by cervical dislocation, their full-thickness skins removed and placed in the previously described Franz diffusion cells." Thus Franz diffusion cells (claims 5 and 8) are used to measure diffusion across hairless mouse skin (claims 13 and 14).

The Patent Office asserts that claim 11 is described in Loftsson et al. in that the chemical reaction between the cyclodextrin and the hydrocortisone is used to affect the diffusion across the skin.

The Patent Office asserts that claim 10 is described in Loftsson et al. in that the formulation is chosen from one of two different cyclodextrins employed throughout the study.

The Patent Office asserts that claims 18 and 19 are described in Table 2 of Loftsson et al., where the standard deviation of the flux needs to be calculated while the flux is an experimentally measured property.

The Patent Office argues that it would have been obvious for someone of ordinary skill in the art at the time of the instant invention to combine the general corticosteroid study of Katz et al. with the cyclodextrin study of Loftsson et al. and the partition study of Tayar et al. because both Katz et al. and Loftsson et al. investigate cortisones as drugs with the added advantage of Loftsson et al. having the feature of cyclodextrins to enhance drug performance; and Tayar et al. is a variation on the type of partition coefficient measured in Katz.

Without agreeing to the Patent Office's characterization of Katz et al., Loftsson et al., or Tayar et al., or admitting that there is even proper motivation to combine them, Applicants submit that none of these references teaches or properly suggests at least choosing at least one model compound and using the model compound(s) to measure diffusion properties across at least one membrane, much less choosing a model compound-excipient formulation based on the measured model compound diffusion; and combining components comprising the at least one pharmaceutical and the excipient package of the chosen model compound-excipient formulation as in present claim 1. In this regard, Applicants wish to point out that the model compound is not the actual pharmaceutical itself, but rather a model compound for the pharmaceutical. In the applied references, it is submitted that none of the compounds studied were used as a substitute for another pharmaceutical of interest. Accordingly, Applicants submit that the patent office has utterly failed to provide the all claim elements necessary to establish a proper *prima facie* case of obviousness. Hence, claim 1 is patentable. Claims 2-5, 8, and 10-24 each add additional features to patentable claim 1, and are likewise patentable.

In summary, the rejection of claims 1-5, 8, and 10-24 under 35 U.S.C. § 103(a) as being unpatentable over Katz et al. in view of Loftsson et al. in view of Tayar et al. has been overcome and should be withdrawn.

Claims 1 and 6-7 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Katz et al. in view of Loftsson et al. in view of Tayar et al. as applied to claims 1-5, 8, and 10-24 above, and further in view of Garcia-Ochoa [Chemistry- A European Journal, 1999, volume 5, pp. 897-901].

The Patent Office asserts that claims 6 and 7 claim the drug formulation method of claim 1, wherein at least one model compound comprises a dye and the diffusion is monitored using fluorescence spectroscopy. The Patent Office admits that Katz et al., Loftsson et al., and Tayar et al. claim the drug formulation process as stated in the instant application, but fail to disclose any use of fluorescence or fluorescence spectroscopy.

The Patent Office asserts that the last sentence in the second paragraph of the methods on page 901 of Garcia-Ochoa states, "^{1}H NMR spectra of 10^{-3}M solutions of HPMO [a fluorescent dye] in D_20 in the absence and presence of 10^{-2}M β-CD [cyclodextrin] (almost saturated solution) were recorded at 500 MHz on a Varian Unity spectrometer at 303K..." The Patent Office asserts that fluorescence spectroscopy is employed to detect the cyclodextrins.

The Patent Office argues that it would have been obvious for someone of ordinary skill in the art at the time of the instant invention to combine Katz et al. in view of Loftsson et al. in view of Tayar as applied to claims 1-5, 8, and 10-24 above, and further in view of Garcia-Ochoa. Garcia-Ochoa is an extension of the cyclodextrin study with the use of fluorescence to more effective monitor cyclodextrin concentration and location.

Without agreeing to the Patent Office's characterization of Katz et al., Loftsson et al., Tayar et al., or Garcia-Ochoa, or admitting that there is even proper motivation to combine them, Applicants submit that Garcia-Ochoa fails to overcome the deficiencies of the combination of Katz et al. in view of Loftsson et al. in view of Tayar et al. as applied to claims 1-5, 8, and 10-24, for example, as discussed hereinabove. For at least these reasons, claim 1 is patentable. Claims 6 and 7 each add additional features to patentable claim 1 and are likewise patentable.

In summary, the rejection of claims 1 and 6-7 under 35 U.S.C. § 103(a) as being unpatentable over Katz et al. in view of Loftsson et al. in view of Tayar et al. as applied to claims 1-5, 8, and 10-24 above, and further in view of Garcia-Ochoa has been overcome and should be withdrawn.

Claims 1 and 8-9 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Katz et al. in view of Loftsson et al. in view of Tayar et al. in view of Garcia-Ochoa as applied to claims 1 and 6-7 above, and further in view of Colarusso et al. [Biophysical Journal; February 2002; volume 82, pages 752-761].

The Patent Office asserts that claim 9 claims the method of formulating a pharmaceutical composition of claim 1, but adds the limitation of recording an image of diffusion of a model compound. The Patent Office further asserts that Claim 8 claims the use of a plurality of diffusion cells.

The Patent Office admits that Katz et al., Loftsson, Tayar, and Garcia-Ochoa teach of method of formulating a drug using a cortisone and a cyclodextrine and fluorescence, but fail to record any images in their studies. The Patent Office asserts that Colarusso et al. illustrate several fluorescent images of cells and the effects of cyclodextrins on them in Figures 1-4 and 6-7.

The Patent Office argues that it would have been obvious for someone of ordinary skill in the art at the time of the instant invention to combine Katz et al. in view of Loftsson et al. in view of Tayar et al. in view of Garcia-Ochoa as applied to claims 1 and 6-7 above, and further in view of Colarusso et al. because Colarusso et al. uses cyclodextrins in analyzing images of cells.

Without agreeing to the Patent Office's characterization of Katz et al., Loftsson et al., Tayar et al., Garcia-Ochoa, or Colarusso et al., or admitting that there is even proper motivation to combine them, Applicants submit that Colarusso et al. fails to overcome the deficiencies of the combination of Katz et al. in view of Loftsson et al. in view of Tayar et al. in view of Garcia-Ochoa as applied to claims 1 and 6-7, for example, as presented in Applicants' remarks hereinabove. For at least these reasons, claim 1 is patentable. Claims 8 and 9 each add additional features to patentable claim 1 and are likewise patentable.

In summary, the rejection of claims 1 and 8-9 under 35 U.S.C. § 103(a) as being unpatentable over Katz et al. in view of Loftsson et al. in view of Tayar et al. in view of Garcia-Ochoa as applied to claims 1 and 6-7 above, and further in view of Colarusso et al. has been overcome and should be withdrawn.

Allowable Subject Matter

Although the present application states that no claims are allowed, Applicants have not found stated grounds of rejection for claim 25, which is therefore presumed to be allowable.

In view of the above, it is submitted that the application is in condition for allowance. Reconsideration of the application is requested.

Respectfully submitted,

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